REMARKS

Claims 1-3, 5-11, 17-23, 36, 44, 85-87, 89, 96-112 constitute the pending claims in the present application. Claims 1, 44, 86, 96, and 99 have been amended. Claim 17 has been canceled, without prejudice. Claims 20 and 21 are withdrawn from consideration. Claims 113-126 have been added. The claim amendments and additions are fully supported by the specification and claims as originally filed. Claims 113-126 are supported by claims 1-11, 22, 23, and 36 as originally filed. No new matter has been introduced.

Amendment or cancellation of claims should in no way be construed as an acquiescence to any of the Examiner's rejections. The amendments to the claims are being made solely to expedite prosecution of the present application and do not, and are not intended to, narrow the claims in any way. Applicants reserve the option to further prosecute the same or similar claims in the instant or in a subsequent patent application.

Applicants wish to thank Examiner Tungaturthi and Supervisor Huff for their time and consideration of the instant application during the telephonic interview with the undersigned on February 20, 2007. The substance of the interview is reflected in the claim amendments and arguments presented in this response.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement is being filed concurrently herewith. Applicants request review and consideration of the references listed on the PTO Form SB/08.

Claim Rejections Under 35 U.S.C. §103

Claims 1-3, 5-11, 18, 19, 22, 23, 36, 96, 99, 100, 101, and 104-112 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Barbas et al. (a) (WO 94/18221) and further in view of Dower et al. (WO 96/40750) and Barbas et al. (b) (PNAS 92: 2529-2533 (1995)) and in view of Cwirla et al. (Science 276: 1696-1699 (1997)) and further in view of Wrighton et al.

(Science 273: 458-463 (1996)) as evidenced by Helms (Protein Science 4: 2073-2081 (1995)). Applicants respectfully traverse this rejection.

Applicants respectfully submit that the references cited by the Examiner, taken alone or in any combination, fail to teach or suggest an immunoglobulin molecule, or fragment thereof, wherein an agonist peptide (such as an EPO or TPO mimetic) replaces a single portion of a complementarity determining region and wherein the immunoglobulin molecule or fragment thereof binds to and agonizes a receptor (such as an EPO or TPO receptor) as claimed in the instant application. In particular, Barbas (a) states that the antibodies described in the application "are particularly well suited for *in vivo* use as a therapeutic reagent for blocking or inhibiting the function of the target molecule which the antibody binds" (see e.g., page 75, lines 29-34). Barbas (a) further provides specific examples of methods for inhibiting platelet gpIIb/IIIa function, methods for inhibiting HIV gp120-mediated events, and methods for inhibiting vitronectin receptor-mediated events (see e.g., pages 78-83) using the CDR replaced antibodies. Accordingly, Barbas (a) teaches methods for designing and using CDR replaced antibody molecules that *inhibit* or *antagonize* receptor function, e.g., by binding to the receptor and interfering with ligand binding. There is **no** teaching or suggestion in Barbas (a) that CDR replaced antibodies could be used to *stimulate* or *agonize* receptor function and/or receptor mediated events. One of ordinary skill in the art would clearly understand that Barbas (a) only discusses antagonists *in contrast* to the pending claims which are directed to agonists. In fact, the skilled person would consider that Barbas (a) teaches away from the subject matter of the pending claims.

The Applicants note with appreciation the telephonic interview held with the Examiner on February 20, 2007 wherein the Examiner acknowledged that Barbas (a) teaches antagonists and not agonists.

The additional references cited by the Examiner fail to make up for the deficiencies of Barbas (a). In particular, Barbas (b) discloses anti-tetanus toxoid Fab molecules that are CDR replaced and bind to DNA. Such antibodies do not even bind to a receptor let alone suggest that such antibodies could be used to *agonize* receptor activity. Furthermore, there would be no motivation for one of skill in the art to combine the teachings of Barbas (a) with the teachings of Dower, Cwirla, Helms or Wrighton. Specifically, Barbas (a) teaches methods for designing and

using CDR replaced antibodies that *antagonize* receptor function while Dower and Cwirla disclose TPO *agonist* peptides and Wrighton discloses EPO mimetics. One of skill in the art would not be motivated to incorporate peptides whose therapeutic value comes from the ability to *stimulate* receptor activity into a system useful for designing antibodies that *inhibit* receptor function.

Furthermore, Applicants note that both Cwirla and Wrighton are directed to the discovery of *small peptides* that can be used as agonists of the EPO or TPO receptor. In particular, both references utilize a phage display library to isolate peptides that *bind* to the desired receptor. These peptides are then synthesized as *isolated peptides* and tested for receptor agonist activity. The peptides are not tested for receptor agonist activity in the context of the phage display. In particular, Wrighton notes that "[t]his discovery may form the basis for the design of *small molecule* mimetics of EPO" (see abstract; emphasis added) and that "*small molecule* EPO mimetics may have desirable pharmacological properties such as oral bioavailability or the ability to be delivered trans-dermally" (see page 463, emphasis added). Why would one of skill in the art want to incorporate the peptides of, for example, Wrighton, into a much larger antibody molecule when Wrighton teaches that the goal is develop small molecule therapeutics for their desirable pharmacological properties? This would be doing exactly the opposite of the teachings of Wrighton. The Helms reference discusses stability and conformational effects of the introduction of sequences into CDR regions and suggests that the introduction of novel sequences into CDRs can significantly *diminish the stability* of immunoglobulins (see e.g., page 2073, abstract; page 2073, second paragraph in second column; page 2073, fourth paragraph in second column; page 2077, paragraph 3 in column 2; etc.). Accordingly, Helms teaches away from the claims as currently pending.

Therefore, one of ordinary skill in the art would not be motivated to incorporate the *small, agonist peptides*, such as the TPO peptides of Dower, Cwirla and Wrighton into the CDR replaced antibodies of Barbas (a) or (b). Furthermore, none of the references provides a suggestion that such a combination should be made nor that such a combination would have any therapeutic utility.

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. *In re Kahn*, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006) Nothing in the cited references suggests inserting agonist peptides into CDR regions of immunoglobulins in order to

agonize receptor function. Accordingly, none of the references cited by the Examiner, taken alone or in any combination teach or suggest the CDR replaced antibodies as claimed in the instant application. In particular, the references relied on by the Examiner merely teach CDR replaced inhibitory antibodies and TPO peptides that are useful as agonists. However, one of ordinary skill in the art would have no motivation to incorporate such agonist peptides into the CDR replaced antibodies disclosed to be useful as receptor inhibitory agents.

Based on the above remarks, Applicants submit that the currently claimed immunoglobulins and fragments thereof are not obvious in view of the cited references in any combination. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. §112, second paragraph

Claims 1-3, 5-11, 18, 19, 22, 23, 36, 44, 85-87, 89, and 96-112 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Specifically, claims 1, 86, 96, and 99 are allegedly not clear for recitation of the phrase "wherein one or more amino acid residues of a CDR are replaced with a peptide mimetic." Applicants respectfully disagree with the rejection. Applicants also do not believe that the rejection is properly applied to claim 44 as the claim does not recite the term "peptide mimetic". However, in an effort to expedite prosecution of the application, claims 1, 44, 86, 96, and 99 have been amended and the amendment is believed to obviate the rejection. In particular, claims 1, 86, 96, and 99 have been amended to specify that a peptide mimetic replaces a single portion of a CDR and claim 44 has been amended to specify that a biologically active peptide replaces a single portion of a CDR. Reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

Claim Rejections Under 35 U.S.C. §112, first paragraph

Claims 1-3, 5-11, 18, 19, 22, 23, 36, 44, 85-87, 89, and 96-112 were rejected under 35 U.S.C. §112, first paragraph, because it is alleged that the application fails to comply with the written description requirement. In particular, the Examiner alleges that new matter was introduced in claims 1, 86, 96, and 99 by the amendments filed on August 31, 2006, specifically that the claims read on "an immunoglobulin molecule of fragment thereof comprising a region wherein one or more

amino acids within the CDR portion can be replaced one or more EPO mimetics OR one or more TPO mimetics OR a combination of one or more EPO and TPO receptors."

Applicants respectfully disagree with the rejection. Applicants also do not believe that the rejection is properly applied to claims 44 or 96, as the claims do not recite the terms "EPO mimetics" or "TPO mimetics". However, in an effort to expedite prosecution of the application, claims 1, 44, 86, 96, and 99 have been amended and the amendment is believed to obviate the rejection. In particular, the amended claims specify that a peptide mimetic, or biologically active peptide, replaces a single portion of a CDR, which is fully supported by the specification, in particular in the examples. Additionally, the amended claims separately recite EPO or TPO mimetics.

Claims 1-3, 5-11, 18, 19, 22, 23, 36, 44, 85-87, 89, and 96-112 were rejected under 35 U.S.C. §112, first paragraph, because it is alleged that the application does not provide enablement for an immunoglobulin molecule or fragment thereof that comprises "replacement of a CDR with an EPO or a TPO or both EPO or both TPO peptide mimetics that do not bind either of the receptors." Applicants respectfully disagree with the rejection. However, in an effort to expedite prosecution of the application, the claims have been amended and the amendment is believed to obviate the rejection. In particular, the claims have been amended to recite EPO mimetics and TPO mimetics in separate claims. Claims 1-36 and 96-98 read on an immunoglobulin molecule or fragment thereof, comprising a TPO mimetic, that binds to and agonizes a TPO receptor, while newly introduced claims 113-126 read on an immunoglobulin molecule or fragment thereof, comprising an EPO mimetic, that binds to and agonizes an EPO receptor. The amended claims now contain subject matter that the Examiner acknowledges to be properly enabled. (See previous Office Action at page 11, point 15.)

Claims 2, 3, 5-11, 18, 19, 22, 23, 36, 97, and 98 are dependent on claim 1 and therefore the amendment of claim 1 is believed to obviate the rejection with respect to these claims. Applicants do not believe that the rejection is properly applied to claims 44, 85-87, 89, 96, and 99 because these claims do not recite the terms "EPO" or "TPO" and request clarification if the Examiner intends to maintain this rejection.

Furthermore, Applicants respectfully disagree with the Examiner's reliance on the Rudikoff et. al., Colman et. al. and Ibragimova references. The Examiner points to these references as demonstrating that changes to protein sequences can have effects on protein stability and function. For example, the Rudikoff and Colman references are alleged to show that changes to an antibody sequence can affect antibody activity including antigen binding function or binding affinity. The pending claims are directed to immunoglobulin molecules comprising a peptide mimetic inserted into a single portion of a CDR. In contrast to the cited references, the binding ability of the claimed immunoglobulins is based on an interaction between the peptide mimetic and another molecule, such as, for example, a receptor. The binding ability of the claimed molecules is not governed by the precise three dimensional conformation of the CDR regions as is the case for conventional antibody-antigen interactions. As opposed to the case of a typical antibody wherein it may be necessary for the six different CDRs to be in the proper conformation relative to each other for proper binding to the antibody target and where a change in the antibody sequence may disrupt the normal conformation, in the present case the antibody is acting as a carrier for a peptide and it is merely necessary for the peptide within the antibody carrier to retain its activity, it is not interacting with the various portions of the antibody carrier molecule. No changes are being made to the peptide mimetic sequence. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Double Patenting

Claims 1-3, 5-8, 18, 22, 23, 36, 44, 85, and 97-112 were provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 8, 10, 11, 16, 26-35, 38-56 of copending Application No. 10/307,724. Applicants request that the Examiner hold the provisional rejections made under the judicially created doctrine of obviousness-type double patenting in abeyance until otherwise allowable subject matter is identified in the instant application. Once allowable subject matter has been identified, Applicants will evaluate the filing of a terminal disclaimer or providing arguments in view of the claims pending at that time.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should any additional extensions of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945** under order number ALEX-P01-054.

Respectfully Submitted,

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